

**Effect of Indol on Hematopoiesis in Dogs Fed Deficient Diets.**

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Previous communications<sup>1</sup> from this laboratory have presented evidence that anemia can be caused in dogs by administering amidopyrine together with a black-tongue-producing diet. Neither amidopyrine alone nor the diet alone caused anemia under the experimental conditions observed. The anemia which resulted from the combination of drug and diet could be cured by administering a yeast preparation which is preventive of the symptoms of black tongue. The uniform effectiveness of amidopyrine under these circumstances suggested that some endogenous aromatic compound might be similarly effective. Indol was selected for trial because it was available commercially and because certain published experimental evidence was at hand which bore on its mode of detoxification (Houssay<sup>2</sup>).

Dogs were kept under standard conditions and were fed the black-tongue diet which has been described previously.<sup>3</sup> The diet was known to cause symptoms regularly in from 5-12 weeks. Anemia occasionally occurred due to the diet feeding alone, but was of such an incidence and degree that it could be ruled out as a complicating factor in the experiment.

*Experiment I.* (Fig. 1.) The black-tongue diet was fed without supplement until the first manifestations of stomatitis appeared. Then one gram of crystalline indol was fed daily in a capsule. A very severe drop in blood levels resulted with striking suddenness. Erythrocyte levels of one million cells or fewer per mm.<sup>3</sup> were encountered frequently and fatalities from acute anemia were not uncommon. If the animal survived the immediate drop in blood levels, there was a distinct tendency toward recovery, as shown by a rise in blood levels in spite of the fact that the indol administration was continued. Control studies in which the same amount of indol was administered to dogs fed a normal diet resulted in no persistent anemia of significant degree.

*Experiment II.* (Fig. 2.) Prolonged experiments were next made in order to establish beyond question the effect of diet on

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<sup>1</sup> Miller, D. K., and Rhoads, C. P., *Proc. Soc. Exp. Biol. and Med.* In press.

<sup>2</sup> Houssay, B. A., *Am. J. Med. Sci.*, 1936, **192**, 615.

<sup>3</sup> Miller, D. K., and Rhoads, C. P., *J. Exp. Med.*, 1935, **61**, 173.

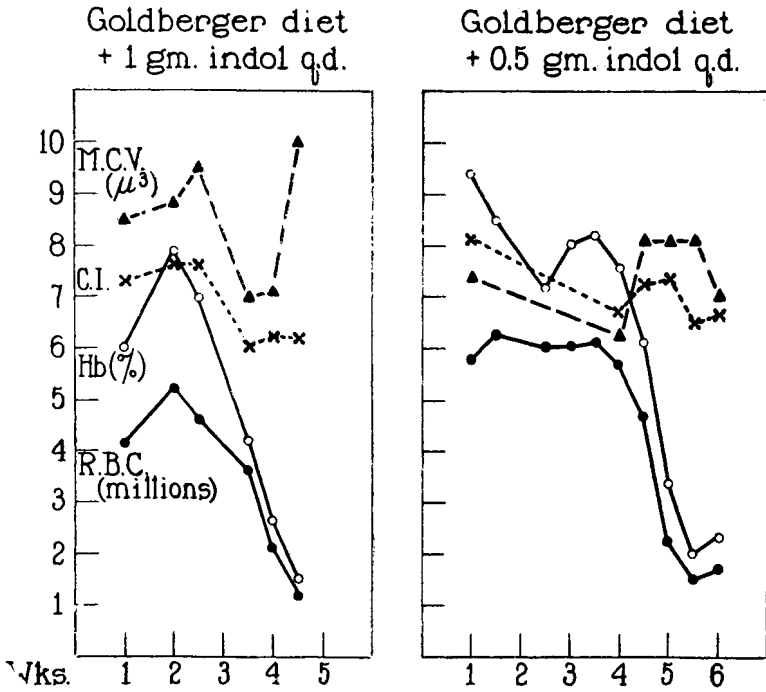


FIG. 1.

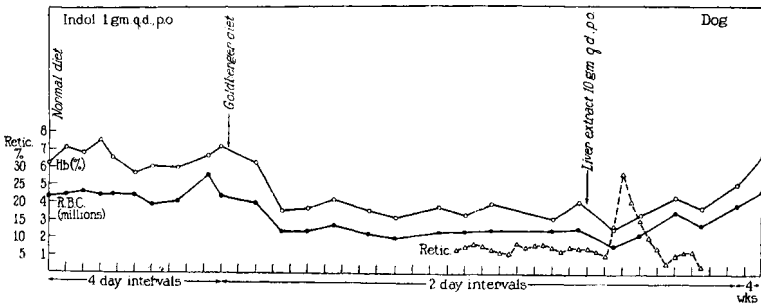


FIG. 2.

the tolerance of the experimental animal to orally administered indol. The drug was fed throughout the study. During a suitable control period, the diet was normal. An irregular mild fall in blood levels occasionally resulted, but was temporary and was overcome as soon as the animal could increase hematopoiesis to compensate for the increased demand. Rare animals were encountered which showed a greater susceptibility to the drug than the average dog. In such instances the dose was adjusted so that essentially normal blood levels were maintained during the control periods. When the

blood became stabilized, the diet was changed to one which regularly caused black tongue. A slow but steady fall in blood levels resulted, accompanied at first by an increased number of circulating reticulocytes, followed by slight increase in the blood levels. As the experiment continued, however, anemia became severe and the reticulocytes stabilized at low levels. Goldberger<sup>4</sup> had shown that liver extract was capable of preventing and curing the symptoms of experimental black tongue. Accordingly the effect of administering liver extract to dogs with the indol-and-deficient-diet anemia was tested. A sharp rise in reticulocytes and improvement in blood levels resulted in every instance in spite of continued indol feeding.

Although ample control experiments had shown that no such anemia ever occurred under the experimental conditions due to the diet feeding alone, further experiments were made to control this factor. Dogs fed diets of milk exclusively showed a similar susceptibility to indol. This was equally true of animals which refused food and became voluntarily malnourished.

Pathological studies showed a very marked extension of active marrow during the anemic phase. The marrow throughout was solid, deep red, gelatinous tissue which showed on histological examination an increased cellularity and a predominance of immature forms.

*Summary and Conclusion.* Orally administered indol is causative of anemia in dogs fed a diet which is causative of black tongue. The same amount of indol does not cause considerable anemia in dogs fed a normal diet. Liver extract is preventive and curative of the anemia.

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#### **Effect of Diet on Susceptibility of Canine Hematopoietic System to Damage by Amidopyrine.**

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The association of amidopyrine administration with the occurrence of acute agranulocytosis of human beings has been described by Kracke and Parker,<sup>1</sup> Madison and Squier,<sup>2</sup> and many others.

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<sup>4</sup> Goldberger, J., and Sebrell, W. H., *Pub. Health Rep.*, 1930, **45**, 3064.

<sup>1</sup> Kracke, R. R., and Parker, F. P., *J. Lab. Clin. Med.*, 1933-34, **19**, 799.

<sup>2</sup> Madison, F. W., and Squier, T. L., *J. Am. Med. Assn.*, 1934, **102**, 755.